Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-33 and 35-42 are pending in the application, with claim 1 being the independent claims.

Claims 1, 2, 8-10, 13, 14, 17-20, 28, 29, 36, and 38-41 have been amended merely to conform to U.S. patent practice. The amendments were not made to overcome a rejection or to further limit the claims. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Rejections Under 35 U.S.C. § 103

In the Office Action dated November 5, 2001, claims 1, 2, 8, 13, 14, 17-20, 28, 36, 38-41 remained rejected under 35 U.S.C. § 103 as allegedly being unpatentable over Wu *et al.*, U.S. Patent No. 5,166,320, in view of Rossi *et al.*, U.S. Patent No. 5,144,019, and Hirsch *et al.*, U.S. Patent No. 5,428,132. Applicants respectfully traverse the rejection.

A. At the priority date of the captioned application (May 18, 1990), there was no motivation for one of ordinary skill in the art to combine the cited documents; the Examiner is using hindsight gleaned from the captioned application to maintain the rejection under 35 U.S.C. § 103.

Legally, determination of obviousness cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention. There must be a teaching or suggestion within the prior art, or within the general

knowledge of a person of ordinary skill in the field of the invention, to look to *particular* sources of information, to select *particular* elements, and to combine them in the way they were combined by the inventor. *ATD Corp v. Lydall, Inc.*, 159 F.3d 534 (Fed. Cir. 1998).

1. Wu et al. generically disclose a gene delivery system for introducing foreign genes into mammalian cells and specifically disclose targeting hepatocytes.

Wu *et al.* teach a gene delivery system for targeting mammalian cells and provide examples of targeting hepatocytes. The gene delivery system comprises a ligand covalently bound to a polycation that is non-covalently bound to a polynucleotide. The conjugate is formed by binding receptor-specific ligands, such as asialoglycoproteins, to polycations. At column 6, lines 1-14, Wu *et al.* state that glycoproteins, antibodies, or polypeptide hormones may be employed as ligands. Wu *et al.* do not teach targeting T-cells or specific ligands that bind to T-cells.

As noted by the Federal Circuit in *In re Baird,* 29 USPQ2d 1550, 1552 (1994), a "disclosure of millions of compounds does not render obvious a claim to three compounds, particularly when that disclosure indicates a *preference* leading away from the claimed compounds." (Emphasis added). The Examiner asserted that Wu *et al.* "[d]iscloses only three types of targeting agents, glycoproteins, antibodies or polypeptide hormones . . . [t]his generic disclosure of three agents does not rise to the level of millions of possible components in which there is no direction to applicants claimed invention." (Paper No. 45, Page 3.) Applicants respectfully disagree.

The generic disclosure of glycoproteins, antibodies or polypeptide hormones in the Wu *et al.* patent cannot not be thought to comprise a small grouping of compounds. The

disclosure of the use of "glycoproteins" as the targeting ligand suggests that *any* protein containing a sugar moiety can be used as the protein targeting ligand in the complex. The disclosure of "antibodies" comprises a group that includes, but is not limited to, immunoglobulin proteins and fragments which bind antigen (Fab fragments), as these latter molecules could also act in a similar fashion as immunoglobulins and retain many of the necessary characteristics of an antibody. Finally, the disclosure of "polypeptide hormones" can assert the use of *any* polypeptide hormone, *or any fragment thereof* which retains biological activity. Thus, contrary to the Examiner's assertion, the disclosure of Wu *et al.* encompasses thousands (and perhaps millions) of different combinations of protein-polycation-DNA conjugates.

Indeed, the success - if any - of the methods of Wu *et al.* appears to be limited to gene delivery using asialoglycoproteins in hepatocytes. The specification, examples, and the claims of Wu *et al.* all point to solving the problem of hepatocyte transfection. In contradistinction, the claims in the captioned application require conjugates that target T-cells. In this respect, Applicants reiterate that the issue presented here is similar to the one presented in *In re Baird*, *supra*, where there was a disclosure of a vast number of possibilities and the preferred examples were distinct from the claimed invention.

2. Wu et al. do not suggest to one of ordinary skill in the art to use Wu et al.'s delivery system for delivering ribozymes to T-cells.

The Examiner has indicated that Rossi *et al.* teach the introduction and delivery of ribozyme genes to CD4+ T-cells with a liposome-ribozyme targeting system to treat HIV infected cells. (Paper No. 45, page 3.) The Examiner has also alleged that it was known in the art that "antibody-polylysine-polynucleotide conjugates [were] advantageous delivery

systems to liposomes." (*Id.*) Indeed, as the Examiner has suggested, Wu *et al.* teach that liposome gene delivery systems have "inherent problems" and that the object of their invention is to provide "new and improved carrier system[s]." Col. 1, lines 46 and 56. However, Wu *et al.* provide no comparative data which demonstrates that their claimed methods and compositions are superior to other gene-delivery methods. They also do not provide that their gene-delivery method works for introduction of DNA into T-cells. That the system works for select applications in hepatocytes is the full extent of the teaching in Wu *et al.*

To indicate that there are general disadvantages associated with the use of one type of gene-delivery method does not provide a suggestion to utilize another type of method. The state of the art was such that virtually all gene delivery systems were characterized by some problems. *See, e.g.*, Verma, I.M. & N. Somia, *Nature 389*:239-42 (1997) (Exhibit A); Anderson, W.F., *Nature 392(Supp.)*:25-30 (1998) (Exhibit B).

Also, even if one particular method (e.g., antibody-polylysine-polynucleotide conjugates) is *generally* deemed superior to another (e.g., liposome-mediated gene delivery) by those skilled in the art, that does not necessarily mean that that particular method is more advantageous for a *particular* application and that it would not have certain disadvantages in particular applications. *See id.* *See also* Hodgson, C.P., *Bio/Technology 13*:222-25 (1995) (Exhibit C). Nowhere in Rossi *et al.*, Wu *et al.* or Hirsch *et al.* is there a teaching or suggestion that ligand-polycation conjugates would be effective for the problem of delivering and introducing genes into cells of the T-cell lineage. "A general incentive does not make a particular result obvious, nor does the existence of techniques by which those

efforts can be carried out." *In re Deuel*, 34 USPQ2d 1210, 1216 (Fed. Cir. 1995). Because there is no particular teaching that leads one of ordinary skill in the art to arrive at the claimed invention, Applicants assert that the claimed compositions and methods are not obvious.

> ***3. Even assuming, arguendo, that in delivering ribozymes to T-cells, one skilled in the art were to look for delivery systems other that those mediated by liposomes, there were many other delivery systems in the art, and Hirsch et al. teach away from the claimed invention.***

In the Office Action dated February 28, 2001, the Examiner stated as follows:

> at the time of Applicant's invention, it was known to make and use antibody-polylysine-nucleotide conjugates for the delivery of and introduction of genes into mammalian cells, taught by the '320 patent [Wu *et al.*], it was known to deliver and introduce ribozymes genes to CD4+ T cells with a liposome-ribozyme targeting system to treat HIV infected cells as taught by the '019 patent [Rossi *et al.*], it was known to deliver and transfect T cells with anti-CD3 antibody-polynucleotide conjugates as taught by the '132 patent [Hirsch *et al.*] and it was known that antibody-polylysine-polynucleotide conjugates where advantageous delivery systems to liposomes because it is difficult to control the leakage of contents of the liposome and to direct cell specificity as taught by the '320 patent and it was known that by noncovalently conjugating the polynucleotides to polylysine it allows for the polynucleotides to not be damaged or altered so successful in vivo endocytosis and expression of said polynucleotide can occur as taught by the '320 patent, so there was clear motivation to arrive at Applicant's claimed invention by the combined teachings of the '019 patent, '132 patent and the '320 patent by creating a ribozyme targeting agent that is linked to anti-CD3 antibody by polylysine.

Paper No. 45.

Assuming, *arguendo*, that in delivering ribozymes to T-cells, one of ordinary skill in the art were to look for gene-delivery systems other than those mediated by liposomes, there is nothing in Rossi *et al.* that would lead one to the ligand-polycation-polynucleotide system of Wu *et al.* Rossi *et al.* teach that alternatives to the liposome-mediated ribozyme delivery methods are cellular transfection methods, calcium phosphate methods, lipofection, electroporation, or the use of a retroviral vector. Col. 6, lines 65-67. Other gene delivery systems known in the art included, for example, DEAE Dextran, cell fusion, gene-gun delivery systems, naked DNA delivery systems, microinjection delivery systems, microbombardment delivery systems, and the antibody-DNA conjugate system of Hirsch *et al.* From a myriad of gene delivery systems, there was no motivation for one of ordinary skill in the art to choose the system of Wu *et al.* to deliver ribozymes to a cell.

The Examiner has opined that there was a motivation to combine the cited documents because it was known in the art that non-covalently conjugating the polynucleotide to polylysine allows for the nucleotide to not be damaged or altered so that successful *in vivo* endocytosis and expression can occur. While Wu *et al.* indicate that the nucleic acid binding component must be capable of binding without damaging or chemically altering the gene (col. 3, line 46), there is no indication in Wu *et al.* that non-covalent binding is *more* effective at preventing this undesired effect than covalent binding. Wu *et al.* only indicate that their method of preventing alteration and damage of the DNA is by non-covalent binding. Col. 3, line 46.

Preventing damage or alteration of the nucleotide to be delivered into the cell is the goal of any gene-delivery method so as to maintain the coding integrity of the gene of

interest. The Examiner has not provided evidence of why this goal would have suggested the claimed invention to one of ordinary skill in the art, rather than other known methods of nucleotide delivery, which can have the similar advantage of not damaging or altering the nucleotide. Moreover, Hirsch *et al.* teach an antibody-DNA conjugate wherein the conjugation is by "directly linking, coupling, binding, . . . either chemically, *electrostatically, non-covalently* or by other techniques such as the production of hybrid antibodies which recognize both the DNA and a target antigen." Col. 2, line 15 (emphasis added).

Thus, given that both Wu *et al.* and Hirsch *et al.* teach gene delivery systems using non-covalent interaction between the DNA and delivery moiety, one of ordinary skill in the art would have been motivated to use the Hirsch *et al.* system - an antibody-DNA conjugate, not the Wu *et al.* system - a ligand-polycation-DNA conjugate. This is because the Hirsch *et al.* system requires less components (does not require a polycation component as by Wu *et al.*), specifically describes *successful* targeting of DNA to T-cells (whereas Wu *et al.* do not teach that their system would work for targeting T-cells), and describes a more current work. (Wu *et al.* has a 35 U.S.C. § 102(e) date of April 22, 1987, whereas Hirsch *et al.* has a 35 U.S.C. § 102(e) date of October 11, 1987, and thus Hirsch *et al.* qualifies as a subsequent "publication" to Wu *et al.*) In other words, Hirsch *et al.* teach away from the claimed invention!

B. At the priority date of the captioned application, one of ordinary skill in the art would not have had a reasonable expectation of success of making and using the claimed invention.

The Examiner has also asserted that one of ordinary skill in the art would have an expectation of success in combining the documents in order to obtain the claimed invention because antibody conjugating methods were known in the art and methods of linking polynucleotides to polylysine were known in the art. Assuming, *arguendo*, that the cited documents suggested the claimed invention (which they did not), there was no reasonable expectation by one of ordinary skill in the art that the claimed composition would be taken up by cells expressing T-cell surface antigens. Wu *et al.*, while providing experimental data for targeting hepatocytes using asialoglycoproteins, provide no indication that their gene-delivery method would be effective for targeting cells of the T-cell lineage using T-cell receptor-specific antibodies. Rossi *et al.* provide no indication that ribozyme genes could be delivered to T-cells using polycation-protein conjugates. Hirsch *et al.*, while teaching antibody-DNA conjugates, provide no indication that the addition of a polycation (which can dramatically increase the surface area, weight and volume of the conjugate) could produce conjugates capable of introducing DNA into cells. As is known by those having ordinary skill in the art, the optimal methods of transfecting cells must be determined empirically on a case-by-case basis because each type of cell responds differently to the methods chosen, hence the multitude of methods and compounds utilized for gene transfer in the art.

In support of the assertion that there was an expectation of success in creating the claimed invention, the Examiner has stated that:

> [T]he '320 patent clearly teaches that 'It is known that most, if not all, mammalian cells possess cell surface binding sites or receptors that recognize, bind and internalize specific biological molecules, i.e. ligands. These molecules, once recognized and bound by the receptors, can be internalized within the target cells within membrane-limited vesicles via-receptor mediated endocytosis.'

(Paper No. 50, page 3.)

Again, the Examiner takes a general teaching in the art and asserts that it is applicable to specific applications. Just because "most" cells have surface binding sites that recognize and internalize specific molecules does not necessarily mean that targeting these sites is suitable for transfection of particular cell types with foreign nucleic acids. For example, certain cell surface binding sites may lead to vacuolization and degradation of the nucleic acid within lysozymes. In addition, depending on the state of the cell, certain receptors may be down-regulated resulting in a reduced number of receptors available for targeting. If the goal of transfection was introducing as much foreign DNA as possible to the target cell, one skilled in the art would likely avoid targeting these down-regulated receptors.

Indeed, at the time of filing, it was known in the art that HIV infection of T-cells causes a loss of CD4 from cell surfaces via Nef, which acts by inducing CD4 endocytosis. *See* Aiken, C. *et al.*, *Cell 76*:853-64 (1994) (Exhibit D). Thus, one of ordinary skill in the art would recognize that the broad and general teachings of Wu *et al.* would not be completely applicable to all cell types and all cell surface targets, particularly in the transfection of HIV- infected T-cells using CD4 as a target.

Applicants assert that the Examiner has "selectively culled" together known elements from the prior art despite the fact that there is no motivation to do so or expectation of success in doing so. As discussed, there is no *particular* teaching or suggestion in any of the documents that would motivate one skilled in the art to combine the other documents to arrive at the claimed invention and there is no expectation of success from the prior art that the compositions of the claims would be effective for introduction of genes cells of the T-cell lineage. Thus, Applicants assert that the Examiner has engaged in improper hindsight reasoning gleaned from the captioned application to arrive at the claimed invention. In view of the above, Applicants respectfully request that the rejection under 35 U.S.C. § 103 be withdrawn.

II. Objections to Claims

Claims 9, 10 and 29 were objected to as allegedly being dependent upon rejected base claims. The Examiner indicated that the claims would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Applicants respectfully traverse the objections.

Applicants thank the Examiner for indicating that claims 9, 10 and 29 are allowable if rewritten in independent form. However, for the reasons provided above, it is Applicants' position that the base claims are nonobvious and thus, claims 9, 10 and 29 need not be rewritten in independent form. It is respectfully requested that the objections be withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Preliminary Amendment is respectfully requested.

Respectfully submitted,

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Attachments
Exhibit A: Verma, I.M. & N. Somia, *Nature 389*:239-42 (1997)
Exhibit B: Anderson, W.F., *Nature 392(Suppl)*:25-30 (1998)
Exhibit C: Hodgson, C.P., *Bio/Technology 13*:222-25 (1995)
Exhibit D: Aiken, C. *et al.*, *Cell 76*:853-64 (1994)

Version with markings to show changes made

Claims 1, 2, 8-10, 13, 14, 17-20, 28, 29, 36, and 38-41 have been amended as follows:

1. (Twice amended) [New] A protein-polycation conjugate[s] which [are] is capable of forming, with a nucleic acid[s] or nucleic acid analogue[s], a soluble complex[es] which [are] is absorbed into a human or animal cell[s], characterised in that the protein component of the conjugate[s] is [a protein] capable of binding to a cell surface protein other than [the] a transferrin receptor expressed by a cell[s] of [the] a T-cell lineage, so that the complex[es] formed [are] is taken up into a cell[s] which expresses a [the] T-cell surface protein.

2. [Conjugates] The conjugate according to claim 1, characterised in that the[ir] protein component is a [preferably] monoclonal antibody or a fragment thereof, directed against the T-cell surface protein.

8. (Twice amended) [Conjugates] The conjugate according to claim 2, characterised in that [they contain] the protein component is an antibody in a form which is directly coupled to the polycation.

9. (Twice amended) [Conjugates] The conjugate according to claim 2, characterised in that [they contain] the protein component is an antibody in a form bound by means of a protein A coupled to polycation.

10. (Once amended) A Protein A-polycation conjugate[s] for preparing the [antibody] conjugate[s] according to claim 9.

13. (Once amended) [Conjugates] The conjugate according to claim 1, characterised in that [the] a polycation component is a synthetic homologous or heterologous polypeptide.

14. (Once amended) [Conjugates] The conjugate according to claim 13, characterised in that the polypeptide is polylysine.

17. (Twice amended) [New] A protein-polycation/nucleic acid complex[es] which [are] is absorbed into a human or animal cell[s], characterised in that [the] a protein component of the conjugate[s] is [a protein] capable of binding to a cell surface protein other than the transferrin receptor expressed by a cell[s] of the T-cell lineage, so that the complex[es] formed [are] is taken up in a cell[s] which expresses a [the] T-cell surface protein.

18. (Twice amended) [Complexes] The complex according to claim 17, characterised in [that they] containing as [the] a conjugate component one of the conjugates defined in claim 1.

19. (Amended) [Complexes] The complex according to claim 17, characterised in [that they] additionally containing a non-covalently bound polycation, which may optionally be identical to the polycation of the conjugate, so that [the] internalisation and/or expression of the nucleic acid achieved by the conjugate is increased.

20. (Twice amended) [Complexes] The complex according to claim 17, characterised in [that they] containing a virus inhibiting nucleic acid.

28. (Twice amended) [Complexes] The complex according to claim 20, characterised in [that they] containing an inhibiting nucleic acid in the form of a ribozyme, optionally together with a carrier RNA, or the gene coding therefor.

29. (Once amended) [Complexes] The complex according to claim 28, characterised in [that they] containing a nucleic acid in the form of a genetic unit consisting of a tRNA-gene as carrier gene and a ribozyme gene arranged within this gene.

36. (Twice amended) Process for introducing nucleic acid or acids into a cell[s] which expresses a T-cell surface protein, by forming [one of] the complex[es] defined in claim 17, which is preferably soluble under physiological conditions, from [one of] the protein-polycation conjugate[s] defined in claim 1 and nucleic acid or acids, optionally in the presence of non-covalently bound polycation, and bringing the cell[s] which expresses the T-cell surface protein, especially T-cell[s], into contact with this complex, optionally under conditions under which the breakdown of nucleic acid in the cell is inhibited.

38. (Twice amended) Pharmaceutical preparation containing as active component one or more therapeutically or gene therapeutically active nucleic acids in the form of [one of] the complex[es] defined in claim 17.

39. (Once amended) [Conjugates] The conjugate according to claim 1, characterized in that said protein is an anti-CD3 monoclonal antibody.

40. (Once amended) [Complexes] The complex according to claim 17, characterized in that said protein is an anti-CD3 monoclonal antibody.

41. (Once amended) [Conjugates] The conjugate according to claim 1, characterised in that the protein component is an antibody against CD3.